DEPARTMENT OF SUMMARIES

TO BE DEVOTED TO DIGESTS OF PROGRESS IN BIOLOGY

While the *Transactions* will continue to be primarily a Journal of research in micro-biology, it is recognized that the field has become so broad as to preclude the possibility of frequent articles in any one of the departments of special interest. Because of this it will be the policy to present, from time to time, supplementary digests of the progress being made in the various fields of micro-biology. It is also proposed to introduce similar summaries of the progress made in some departments not represented in our articles of research. This is done with the feeling that such reviews will increase the permanent value of the *Transactions* to all who may not have access to a large list of technical biological journals, nor the time to make the survey for themselves.

RECENT PROGRESS IN SOME LINES OF CYTOLOGY.

MICHAEL F. GUYER, UNIVERSITY OF CINCINNATI.

When one realizes that not only the ultimate details of all plant and animal structure, but that practically every biological manifestation of function and process from the flow of thought to the pathology of cancer resolves itself in last analysis into a problem of the living cell, the temerity of any one attempting to review the whole field judicially becomes evident. Merely to confront the literature of the subject, is to face a veritable deluge of new facts and changing ideas. There is today a decided leaven of unrest at work among the anatomists and physiologists of the cell which finds expression in a general dissatisfaction with older views, in much contradiction among current interpretations, and in a realization of the transiency of any conclusions until more delving has been done in the field of bio-chemistry.

The old adage that he who would write with elegance must give his days and nights to the reading of Addison, might well be paralleled biologically by the statement that he who would understand modern problems of the cell, must give his days and nights to the study of the physico-chemical conditions of protoplasm.

THE COLLOIDAL NATURE OF PROTOPLASM.

Inasmuch as our current problems in cell function center about the physical nature of protoplasm, we may well begin our survey at this point. We must discriminate at the outset between two classes of substances found in the cell, viz., crystalloids and colloids. Crystalloids are, for the most part, crystalline substances of a low molecular weight which in solution diffuse readily through animal membranes. Examples are salts, sugar, urea, etc. Colloids *(kolla; glue)* are generally amorphous substances of high molecular weight which diffuse slowly in liquids and which penetrate animal membranes very poorly or not at all. They do not form true solutions as do the crystalloids and are likely to be viscid. Examples are gelatin, the albumins, glue, gums and the like.

The line of distinction between crystalloids and colloids is not as fast as was originally supposed, for numerous transitions have been found to exist. The reason for this is apparent when we stop to realize that as a matter of fact when we use the terms colloid and crystalloid, we are not classifying substances, but *states*. Albumin, for example, which generally exists as a typical colloid, can nevertheless be obtained in crystalline form, and conversely, the commonest salts may be put into a colloidal form. Undoubtedly many if not all substances may exist now in the crystalloidal now in the colloidal state. The importance of discriminating between the two states lies in the fact that a given substance in colloidal form usually possesses entirely different properties from the same substance in the crystalloidal form.

Just as crystalloidal and colloidal states intergrade, so no sharp distinction can be drawn between the so-called colloidal suspensions and the colloidal solutions. In general, colloidal states resulting through the mixture of a solid and liquid phase as, for instance, a finely divided metal* and water form true suspensions. These are

*Colloidal suspensions of metals are prepared by sending an electric current through electrodes composed of the metal of which the suspension is desired. Platinum, for example, has been much utilized. The electrodes are immersed in a dish of pure water and the current turned on. A cloud of extremely fine particles of the metal streams out into the water and remains suspended.

non-viscous and are easily coagulated by salts, whereas, through the mixture of two liquid phases, a viscous, easily gelatinized type of colloid results which is not so readily coagulated by salts. Wolfgang Ostwald has recently characterized these as *suspension colloids* and *emulsion colloids* respectively.

Living matter is characterized by its richness in colloids of the emulsion type. Protoplasm is really an aggregate of colloids holding water for the most part, in which are contained certain salts and non-electrolytes (crystalloids in general). These colloids form a comparatively coherent, permanent and definitely arranged substratum by which the distribution of the other substances is largely determined.

It is the colloidal part of an organized body, such for example as gelatin, that permits of the swelling it may undergo by the imbibition of water. Such a colloid can, under favorable conditions, absorb into its interior a large quantity of water, shrinking again as the water is expelled. The water in such cases of imbibition must become evenly distributed amongst the organized particles of the colloid, pushing them farther and farther apart by the increasing envelopes of liquid which surrounds each one until the limit of imbibition is reached.

Colloids may exist in a liquid or semi-liquid form also. In the case of gelatin, for example, if the jelly-like mass which results from the absorption of water is heated, a fluid condition results. Many colloids remain fluid at ordinary temperatures. In such cases the constituent particles have been sufficiently separated to move freely past one another, yet as a system they still retain a certain degree of organization. Thus colloidal substances may exist in a jelly-like, a coagulated, or a precipitated form, or they may be in pseudo-solution or fine suspension. That they persist as particles even in the fluid condition has been determined both inferentially and by observation. Theoretically their behavior can be explained on no other basis, and observation of such fluids under the microscope shows that their manner of diffracting light is such as could only be brought about by a series of particles held in suspension in a fluid. These particles must not be confused, however, with molecules; in general they must be aggregates of molecules. This is shown among other ways by their enormously greater molecular weights. Their activities are essentially physical rather than chemical in nature.

In fluids, the particles of the colloid, whether organic or inorganic (such as finely divided metals), usually exist in the form of *suspensions* rather than true *solutions*. We know this because substances in true solution alter the freezing point and boiling point of the solvent, but colloidal substances change these points little if at all. Furthermore, solutions of crystalloids show an osmotic pressure, their diffusibility depending upon the smallness of the dissolved particles. On the contrary, mere suspensions show no osmotic pressure and typical colloids behave in this manner. In the case of the colloidal constituents of living cells, which cannot be tested by freezing and boiling, we have to resort to this more round-about method of determining whether or not osmotic pressure exists. As a matter of fact it seems in some instances that proteins may be, in part at least, in the form of true solutions. For example, Starling has shown that the proteins dissolved in blood serum have some osmotic pressure and this in an amount that is far from being negligible. By direct measurement he found an osmotic pressure of 30 - 40 mm. of mercury.

It is customary to speak of colloids in the liquid state as *sols* and in the more solid conditions as *gels*. Protoplasm, therefore, since its fluidity is due to water, is a *hydrosol*. Like many other sols protoplasm passes readily into the gel condition, becoming a *hydrogel*. Of colloidal gels there are two fairly well defined classes, viz., *reversible* and *irreversible*. In the first class, reversal of the condition which produces the gel causes it to return to its former state. For instance, the hydrosol of gelatin sets to a hydrogel upon cooling, the process being reversed by heating. In the second class, no return to the former state is produced by reversing the conditions. As it is probable that the irreversible gelations are associated with a change in the colloid itself, the colloid is frequently said to be "denatured" by the conditions acting upon it.

Protoplasm, so long as conditions for vital phenomena persist, presents a remarkable degree of reversibility, many of its colloids passing readily from the sol to the gel state and back again. Most protoplasmic structures seemingly originate through the setting or coagulation of liquid colloids. In all probability, when we are dealing with cell membranes, spindles, astral radiations, alveoli and various other cell structures we are dealing essentially with conditions of gelation. When such are seen in the living cell it is presumable that they are of the reversible type. What is seen in a fixed cell is no sure criterion of what actually exists in the living cell. Traube showed long ago that where two liquid colloids come into contact under certain conditions, solid membranes may be formed. Agents which tend to bring about an irreversible gelation of protoplasm tend to bring life to a standstill. For example, heating proteids much above 45°C. produces such a permanent gelation. It has been suggested that the heavy metals are poisonous to living cells because they transform the proteins into irreversible gels.

While we may speak of protoplasm as a hydrophylic (i. e. water-holding) colloid, it must not be forgotten that it also contains small quantities of various crystalloids (salts, etc.). This means that the chemical reactions of protoplasm invariably occur in a liquid which is really a dilute solution of electrolytes. As is well known, electrolytes when in solution dissociate more or less into their constituent ions. For example, common salt, NaCl, when dissolved in water exists in parts as free Na ions and free Cl ions, and in part as molecular NaCl, the degree of dissociation depending upon concentration of the solution. The ions thus freed in solutions become charged electrically in the process of dissociation. The electro-negative ions are called the *anions,* the electro-positive, the *cations.* In the case of solutions of sodium chloride (NaCl), for instance, the released sodium ions bear positive charges of electricity and are therefore the cations; the freed chlorine ions bear negative charges and are the anions. Ions may consist not only of charged atoms but of charged groups of atoms (radicals) as well. Processes of ionization occur in all solutions of electrolytes. It is important to bear the electrical charge of the atoms in mind for this introduces additional factors into the reactions of living substance. Many workers believe that the physiological actions of not a few substances such as those of the common salts are due to these electrical charges borne by the ionized particles and not to the chemical nature of the particles themselves.

It is now an established fact that colloidal particles, as existing under the conditions found in living matter, also bear electric charges. The individual colloid particle although really composed of many atoms or molecules behaves as a single charged particle, as far as its electrical charge is concerned. Picton and Linder, Hardy, and others have shown that the nature of the charge, whether positive or negative, depends both on the nature of the colloidal particle and of the fluid medium in which it is suspended. In general acid colloidal particles are electro-negative, and alkaline colloidal particles, electro-positive. Moreover it has been determined that the charge of the particle induces in the surrounding water or other fluid medium the opposite kind of charge. For example, if the particle is negative, the surrounding medium is positive. Furthermore, the number* of negative or positive charges is proportionate to the surface of the particle. When two or more particles are thrown together, whether by mechanical means, heat, electric current, or internal chemical changes in the colloids themselves,—in short by any means whatever—if the particles coalesce there is a reduction of surface; that is, the amount of surface of the coalesced particles is much less than the sum total of the surfaces of the original particles. Hence there must be an entire readjustment of the electrical conditions. Conversely, as Bredig has shown, when the electrical state of colloidal suspensions are disturbed in any way there must be a corresponding re-arrangement of the colloidal particles. For instance, when the density of the charge of the particles is diminished, aggregation leading to coagulation is brought about; when the density of the charge is increased, a still finer division of the particles is produced. Either change might occur as a result of chemical changes in the particles themselves or in the conditions surrounding them.

With these facts in mind we are now in position to understand something of the conditions which are productive of gelation in colloidal fluids. Hardy, using a sol of proteid has shown: (1) That

*The charge is measured in terms of the electrical unit which the physicist calls the *electron* a gel is produced by the addition of electrolytes, but not by the addition of non-electrolytes unless they act chemically; (2) that the gelation produced by electrolytes is due to the electric charge carried by the ion, inasmuch as identical results follow the use of an electric current from a battery; (3) that the signs of the electric charges carried by the ions (+ or —) determine the movements of the colloidal particles either keeping them in suspension as a sol or causing them to fall into the gel condition (e. g. a sol having its colloidal particles negatively charged will pass into the gel state if + ions are added or if the + electrode of a battery is introduced).

These results indicate the importance of electrically charged particles of any kind in the life of the cell and tend to clarify some of the puzzling phenomena of protoplasmic activity. We can on such a basis readily understand the rapid changes in the consistency of protoplasm—changes from more rigid conditions to those that are more fluid, and *vice versa*. Judging from the experiments of Hardy they may be looked upon as due to changes in the state of the colloids of the cells, which in their turn are determined by the ions set free as a result of chemical changes in the cells.

As a very recent biological application of our knowledge of colloids and the charges they bear may be cited a report of McClendon[1] on the formation or the non-formation of the so-called "fertilization" membrane of the Echinoderm egg. At the time of beginning development a substance comes to the surface of the egg which according to McClendon bears a positive charge, that is, it is basic. The jelly which surrounds the egg, however, is acid, bearing therefore a negative charge. When the two substances come in contact at the surface of the egg they precipitate each other, thus forming the fertilization membrane. By washing away all the jelly before the beginning of development the formation of the membrane is prevented, although development proceeds normally.

There are apparently two special properties of colloids upon which the possibility of forming the definite structural arrangements seen in cells depends:

1. *Science*, March 10, 1911, P. 387.

1. Their tendency to form aggregates and coherent systems of various kinds (gelation, coagulation and changes in state of aggregation generally) and,

2. The electrically charged nature (+ or —) of the colloidal particles themselves. This leads adjacent particles or their aggregates to repel or to attract one another electrostatically. The mutual repulsion of particles appears, indeed, to be one of the chief factors on which the stability of the colloidal system depends.

On the first property depends the formation of the various colloid aggregates in the cell and the particular structure of these aggregates. The second apparently determines in large part the relative disposition assumed by the aggregates within the cell. (Ralph S. Lillie[2] has made an application of this principle to the distribution of the nuclear aggregates or chromosomes in the cell during division). These two properties are closely related as can be demonstrated by altering either of them. Coagulative changes in a sol are brought about, as we have seen, if the particles through any disturbance are caused to lose all or a part of their mutually repellent surface charges. Under such conditions surface tension prevails and adjacent particles coalesce. It is probable that slight and reversible changes in the state of the aggregation of the cell colloids are of constant occurrence in living protoplasm, and are responsible for various of the physiological phenomena observed.

Although our knowledge of the pure physical chemistry of the colloids in the cells is still far from complete, application of the facts already known have been made by many workers in attempting to explain various life phenomena.

Space will not permit of an extended review of these cases but a few representative ones will give some indication of the wide possible application of the principles.

Loeb and Mathews particularly have in various papers insisted on the probable physiologic importance of electrical charges carried by ions, in contradistinction to the specific chemical nature of the constituents which bear such charges. Mathews[3] goes so far as

2. *American Journal of Physiology*, XV, 1905, P. 46.

3. See particularly his papers in *The American Journal of Physiology* for 1904 and 1905.

to say in a comparatively recent paper that "Physiological action is dependent upon electrical state and stability of the ion, and is independent of chemical composition except as the chemical composition may influence its velocity and weight." From his experimental work he deduces a formula according to which he believes the action of any given salt on protoplasm may be approximately predicted. Without going into detail it may be said that he has had to take into account such factors as,—(1) The concentration of ions; (2) The sign (+ or —) of the electric charges of the ions; (3) The modification of the action of the ion due to its velocity and weight (other things being equal, the faster it moves the more powerful it is; the slower or heavier the less powerful); (4) Its electrical stability or what he calls ionic potential* (this he emphasizes more and more in his later publications). He believes that he has established in general that all anions have a stimulating effect, all cations a depressing effect on living matter. Whether any salt stimulates or depresses, therefore, depends upon the relative efficiency of its anions and cations.

Another interesting suggested application of our knowledge of colloidal phenomena is as an explanation of the long standing problem of nerve conduction. Nerve substance is in part at least a colloidal sol, and Mathews in particular, has adduced evidence to show that the progression of an impulse may be due to a wave of gelation sweeping along the nerve. Years ago Darwin found in certain insectivorous plants (Drosera) that if one part of a leaf were stimulated an impulse traveled across to the other side and caused movement. As the impulse progressed he noted that the cell was traversed by a wave of cloudiness due to a fine precipitation which ran together into drops and then re-dissolved. Furthermore, he found that this activity was prevented by ether, chloroform, CO_2 etc., just the substances which produce anaesthesia in animals.

---

*Mathews defines ionic potential as the tendency of any ion or atom to change its electrical state. He at first made use of the method of determining it by means of the solution tension of metals (i. e. in terms of the sum of the work necessary to transform one atom of metal into one gram ion in the same space) but later found he could employ other methods. As justification for applying the idea to protoplasmic activities he cites the evidence of the chemists Bodländer and Abegg that ionic potential is one of the chief factors in determining chemical affinity.

The conditions which prevail in the transmission of a nerve impulse afford at least a very suggestive parallel. As applied to the nervous condition the idea would be that the nerve colloids readily form reversible gels and the nerve impulse is due to a progressive gelation of these colloids. Anaesthetics, possibly because of their solvent action on fats, are presumed to prevent this gelation.

R. S. Lillie has shown the plausibility of regarding the contractions of the swimming plates of Ctenophora as due to reversible colloidal gelations and suggests possible extensions of the idea to other forms of protoplasmic contraction. He has also made interesting suggestions as to the applicability of the principles governing colloidal phenomena to various features of cell division[2]. He found, for example, that by the use of mutually repellant groups of floating magnetized needles, exposed to the attractive or repulsive action of magnetic poles, many features in the arrangement of the chromosomes in cell division could be simulated, particularly the positions taken by spireme figures, and the arrangement of the chromosomes in the equatorial plate stage of normal and of tripolar mitosis. He regards certain features of mitosis, at least, as due essentially to mutual electrostatic repulsions among the chromatin particles.

Another promising line of work has been the use of various colloidal suspensions of metals in the *role* of enzymes. Since the fundamental problems of the metabolism of the cell are at the basis of all life phenomena, and inasmuch as these processes are intimately involved at all stages with enzymic processes, any new light on the enzymes is likely to be of very great value. Enzymic activity is at bottom presumably a matter of catalysis. This idea becomes all the more acceptable when we realize that many fermentative processes can be strikingly paralleled by colloidal suspensions of finely divided metals. Catalysis is seemingly purely a matter of contact action, changes being brought about in a chemical compound by an agent which itself is recoverable at the end of the reaction in an unaltered state, and undiminished in amount. Bredig goes so far as to call certain colloidal suspensions "inorganic ferments." This is because such suspensions are capable of catalysing many

2. *Loc. Cit.*

chemical reactions that may also be catalysed by ferments of cell origin, and in an identical way. For example, colloidal suspensions of platinum have the same power as many ferments of catalytically decomposing hydrogen peroxide into water and oxygen. As in the case of the ferments, this metallic substance is active in exceedingly small quantities. Thus 1 gram atom of platinum (94.8 grams) diluted with 70,000,000 liters of water is still able to accelerate the decomposition of more than a million times its amount of hydrogen peroxide. That is, 1 cubic centimeter of the suspension, containing only one-three hundred thousandth millegram of platinum still shows the so-called fermentative properties. The true organic ferments themselves can scarcely rival this in minuteness of the amount necessary. As is the case with true ferments, these metal sols are very sensitive to heat and various other agencies which inhibit fermentative processes. The parallel is so close that some investigators have expressed the belief that true ferments are colloidal sols which operate in much the same way as do the metal sols. A few illustrations of this parallelism may not be without interest. The oxidation of alcohol to acetic acid by *Mycoderma aceti* can be paralleled by the use of finely divided platinum. Dilute oxalic acid is decomposed by certain fungi, likewise by powdered palladium, platinum, etc. The oxidation of pyragallol is accelerated by the ferment laccase. The same result may be obtained by means of colloidal platinum. Rayman and Sulc have shown that the inversion of cane sugar can be brought about by the action of finely divided metals. On the one hand, oxydase splits hydrogen peroxide into water and atomic oxygen, invertase inverts cane sugar, zymase ferments sugars; on the other, platinum black will do the same. Not only do these metallic suspensions accelerate hydrolysis, but they, like many enzymes, may also show reversibility of action, synthesizing the original substance in the presence of an excess of its cleavage products. Thus Nielsen[4] has apparently by means of platinum black paralleled very closely the activities of the fat splitting enzyme lipase; for he was able to produce hydrolysis of ethyl butyrate into butyric acid and ethyl alcohol and conversely, to

4. *American Journal of Physiology*, 1904.

synthesize these two products into ethyl butyrate again. He has been equally successful in experiments on certain carbohydrates.

As a final example of some of the general lines along which various investigators are attempting to apply our knowledge of colloidal phenomena may be cited an interesting series of experiments by Martin H. Fisher[5] in which he seeks to show both the quantitative and the qualitative importance of colloids in the regulation of the water content of the cells of various tissues. Starting with the fact that the living organism is built up chiefly of hydrophilic (i. e. water absorbing) colloid materials he has devised experiments to show that the behavior of living protoplasm in the quantitative absorption of water is not essentially different from that of simpler non-living hydrophylic colloids such as gelatin or various albumins, nor does it differ qualitatively from these when subjected to parallel series of external conditions such as the effects of various alkalies, acids and salts. He shows, for instance, that living protoplasm can be made to take up or give off water by the same conditions which make gelatin of fibrin give off or take up water. In Fischer's theory, which he terms a *colloidal absorption theory* we find a distinct challenge to the older and prevailing *osmotic pressure theory*. He rejects the whole idea of semi-permeable membranes which is the main stay of the pressure theory. While such workers as Pfeffer, Hofmeister, Durig, Höber, Hamburger, Overton, and Pauli have recognized colloidal absorption as a factor, they have considered it as incidental or of secondary importance, and of utility principally in explaining some of the various exceptions which arise in the applications of the osmotic pressure theory. The questions involved are of such fundamental importance in the functioning of the cell that we may well consider the matter under a special heading, brief though our discussion must be.

The Question of Semi-permeable Membranes.

How to account for the passing of water and substances in solution into and out of the cell during nutritive exchanges, secretions, lymph formation, etc., has long been a puzzling problem. It soon

5. Oedema; A Study of the Physiology and the Pathology of Water Absorption by the Living Organism. John Wiley & Sons, N. Y.

became evident that van't Hoff's laws for osmotic pressure of substances in solution (paralleling the laws of gases) would not hold for living cells, at least in the purely mechanical way which prevails in non-living matter. Physiologists found it necessary to qualify their views of the osmotic nature of the process by using such terms as "selective secretion" "selective absorption or diffusion" and the like, the "selection" depending upon unknown peculiarities of cellular structure or activity. Many workers have come to the conclusion that the phenomena must be due to the existence of semi-permeable membranes—that is, membranes which are permeable to water but not to molecules of the substances in solution or to only certain of these—at the periphery of the cells.

This membrane is not to be confused with the ordinary visible cell wall, since if it exists at all it must also be present in cells devoid of a visible wall. It is regarded by the advocates of this theory as a lipoidal (i. e. fat-like) plasma membrane. It must be recognized at the outset that its existence is one of theoretical necessity rather than something optically demonstrable, unless one identifies it with an ordinary surface-tension film, but its postulated properties are not in keeping with this latter simple physical conception. However this may be, it is a fact that living cells in general show a high degree of physical impermeability to many diffusible substances. The turgor so characteristic of plant cells, for example, is regarded as direct evidence of this fact, since it is due, presumably, to the osmotic pressure of crystalloid substances dissolved in the cell sap. Under such conditions substances in solution in the cell cannot be discharged, although water may pass freely to and fro, nor can substances in solution outside the cell pass in. How then is the exchange of soluble substances effected by the cell? To meet the necessities of the case it is inferred by some that a plasma membrane ordinarily impermeable undergoes periods of permeability. With this in mind various investigators have set about finding the factors which determine and control these temporary lapses of impermeability.

---

6. See especially his paper "The General Biological Significance of Changes in the Permeability of the Surface Layer or Plasma-Membrane of Living Cells. *Biological Bulletin,* XVII, 3, Aug. 1909.

R. S. Lillie[6] enumerates as such factors, the effects of electrical or other stimulation, the influence of internally developed carbon dioxide, and a large class of foreign substances, particularly such as exhibit the property of dissolving or being dissolved in fats. He regards it as probable that food materials enter the cells at times of such permeability yet, as he points out, in both absorption and secretion the relative rates at which many of the substances in solution make their entrance or exit from the cells are largely independent of the laws of purely physical diffusion.

As visible illustrations of the loss of diffusible materials from the cell due to what the advocates of this theory regard as increase of permeability of a surface membrane, may be cited the discharge of pigments during cytolysis or, conversely, the inability of many dyes to enter living cells.

Lillie has performed numerous experiments and adduced much evidence in support of the membrane theory as applied to various problems. He considers, for example, that a temporary and readily reversible increase in the permeability of the plasma membranes is responsible for the phenomena of stimulation in irritable tissues. As to why increase of permeability should correspond to stimulation and decrease to inhibition he answers as follows: "It is assumed that during periods of increased permeability the loss of carbon dioxide from the cell will be more rapid than normal; the energy-yielding oxidative reactions of which this substance is the end-product are thus accelerated as a direct consequence of the increased rate of removal of the reaction-product from the system; hence the increased contractile activity or other energy manifestation during stimulation. Conversely, decrease of the normal permeability means decreased loss of carbon dioxide and hence retarded oxidation and energy-production; stimulation is more difficult at such times because of the greater difficulty of increasing the permeability to the critical degree required. This general view ascribes primary importance to the plasma membrane as probably the chief means by which the velocity of the oxidative energy-yielding reactions in the cell is varied."

The rhythmical action in such tissues as cardiac muscle he believes is due to a regular alternation of periods of increased and decreased permeability. Again, he regards the initiation of cell division as ascribable likewise to a periodic change of permeability and the consequent interchange of diffusible substances and cites evidence to show that the rhythm of the mitotic process is accompanied by a rhythm of alternate increase and decrease of permeability or at least of factors which he regards as causing increase and decrease of permeability. Concerning the manner in which increase in permeability initiates mitotic division he has this to say: "The main factors in producing this effect are in my opinion two: first, a disturbance of chemical equilibrium due to an increase in the rate at which certain metabolic products (probably chiefly carbon dioxide) are lost from the cell; this is an effect similar to that which, on the general theory of stimulation outlined above, underlies the chemical effect of stimulation in muscle. The precise effect of such a change will of course vary from cell to cell. Second, a definitely localized increase in the general surface tension of the cell in consequence of a loss or lowering of the electrical surface polarization." Lillie looks upon the existence of a plasma-membrane possessing but temporary periods of permeability as an indispensable attribute for the preservation of the chemical organization of the cell. Inasmuch as he has stated his point of view concisely in a recent paper he may be directly quoted: "In the specific metabolism of any animal the protein and carbohydrate food materials are split respectively to amino-acids and sugars, both highly diffusible substances; and many other diffusible products important in metabolism are formed by oxidation or hydrolysis. These substances must not be lost from the cell. It is plain that any specific organism must exhibit a constant and specific metabolism—is indeed the product or the manifestation of this. Now the existence of specific metabolic processes in any cell requires the presence of many interacting substances in proportions that must not vary widely from a constant mean; in other words, constancy in the character of its metabolic processes is essential to the specificity of a particular cell. Its protoplasm may be regarded as a mixture of diverse yet constantly present substances in an approximate chemical equilibrium of a highly complex order. Any such constancy of composition, implying constancy in the conditions of equilibrium, would be impossible in a system not very completely isolated from its surroundings. In the cell this isolation is due to the presence of an impermeable surface film. A marked degree of impermeability to the great majority of its diffusible contents is thus indispensable to the continued existence of a highly complex heterogeneous system like the cell."

The semi-permeable membrane or osmotic pressure theory is not going unquestioned, however, for as I have already indicated, Martin H. Fischer[5] has made an arraignment of the whole idea. He objects that such membranes are not optically demonstrable, that their existence lies only in presumed hypothetical necessities and believes that the phenomena concerned are explicable on other and simpler grounds. He points out the fact that formation of "precipitation membranes" in physico-chemical experiments (to which formation of plasma membranes by living protoplasm is supposed to be analogous) is by no means a universal occurrence but that on the contrary the phenomenon is one that happens only under special conditions. Since no known cell is impenetrable to all dissolved substances in the protoplasm or in the surrounding medium of the cell he argues that if we maintain the view of partial permeability, that is permeability to some substances and not to others, then every substance becomes a special case because there is "little apparent connection between the kind of substances that are exceptions to these laws of osmotic pressure." What he is protesting against in reality is what he considers the great overrating of the osmotic theory as an explanation of biological phenomena. For he goes on to say, "I am not maintaining that the laws of osmotic pressure *may* not account for *some* of the phenomena observed in at least *some* cells." He sees "little reason for accepting the osmotic theory as of paramount or even great importance in the explanation of the ways and means by which tissues absorb or secrete water." He would explain this process on the basis of the hydrophylic nature of the colloids of the cell just as one must ex-

5. Loc. Cit.

plain the absorption and secretion of water by powdered gelatin or fibrin on this basis. Inasmuch as all colloids do not react in the same way either qualitatively or quantitatively toward solvents and solutes, and since in the cell various colloids exist, inequalities in the amount of water or solutes held by different tissues, or in different parts of the same cell is readily explicable. The red corpuscle, for example, is a mixture of at least four if not more colloids. There is first the stroma which is probably largely protein in nature, and mixed with it are at least two known lipoids, lecithin and cholesterin, the three enumerated being, in varying degrees, of the hydrophylic type. The two lipoids are good solvents of such substances as chloroform, ether and alcohol. Lastly haemoglobin, although easily obtainable in crystalline form, exist in the corpuscle probably in the form of a colloid but one which has no affinity for water, that is, it is not hydrophylic but "hydrophobic." Likewise other cells possess differences in colloidal constitution—variations in the kind and amounts of colloidal proteids, colloidal lipoids, colloidal carbohydrates, etc.,—and we should, therefore, expect to find corresponding differences in their behavior towards solvents and solutes as regards absorption and secretion.

Fischer finds with tissues as with fibrin and gelatin, that acids and alkalies are the substances most capable of altering the affinity of the hydrophylic colloids for water. Any condition which causes or increases the production or secretion of acid (or alkalies) in the cell, for example, leads to an increased imbibition of water—which when exceeding normal bounds receives a special name such as plasmoptysis or oedema—because acids increase the affinity of the hydrophylic colloids of the cell for water. Carbon dioxide behaves as an acid in this respect. Any conversion of cell colloids having but little affinity for water into hydrophylic types would of course have a similar effect. Lack of oxygen is in the same category inasmuch as Araki has shown that under such a condition lactic acid is produced in the tissues.

Conversely the imbibition of water, that is, the development of oedema, is prevented or diminished by all substances such as salts which decrease the affinity of the hydrophylic colloids for water.

The concentration of the salts in solution in the cell, therefore, is as important factor in determining the aqueous content.

Fischer further points out that we must discriminate sharply between the absorption or secretion of the solvent and the absorption or secretion of the substance dissolved in it, for although the two may be frequently associated they are by no means identical processes. In handling the question of the secretion and absorption of solutes and the retention of them in different proportions in different cells or in different parts of the same cell he makes use of the laws of *simple solution,* of *adsorption* and of *partition.* For example, he regards the retention of haemoglobin in the red corpuscles as largely a matter of adsorption, the stoma being the adsorbing material. The conditions are seemingly parallel to various dyeing processes which have been shown to represent adsorption phenomena, and he has devised experiments to show that just as the degree of adsorption in dyeing may be varied or prevented by the use of various mordants, precipitants, fixants and bleaches, so by a similar use of acids, bases, salts, colloids of various kinds, heat, etc., the combination between haemoglobin and stroma may be increased or decreased. Speaking of the relationship between different colloids he goes on to say "Not only may the individual adsorption characteristics of any group of colloids toward a single other one (hemoglobin in this case) be different but they may mutually affect each other and so alter each other's adsorption characteristics. Lecithin and cholesterin, for example, have properties which allow them not only to share in, or modify the ordinary adsorption phenomena, as exhibited by the protein constituent of the red blood corpuscles, but through their lipoidal character they may not only absorb substances which the rest of the corpuscle cannot take up, but they may be affected by means which do not affect the rest of the blood corpuscle."

As to the third law, he continues, "The law of partition becomes prominent as soon as the dissolved substance is either more or less soluble in some substance contained within the cell than in the solvent surrounding the cell. Hence the special ease and rapidity of absorption of substances readily soluble in fat-like bodies (lipoid-soluble substances) by cells containing such lipoids. In this enormous difference between the solubility of substances in water and in the fat-like bodies, both as to rate of solution and absolute amounts dissolved (coefficient of partition), we can find the explanation not only of the rapidity with which the lipoid-soluble substances enter the cells, but also of the large amounts that may be absorbed."

"When we consider protoplasm simply as a mixture of different colloids (proteins, fats, carbohydrates), and consider the special characteristics of absorption that arise out of such a mixture not only as regards water, but as regards substances dissolved, or pseudo-dissolved (colloids) in it, it seems to me that we account without difficulty, even without membranes, for all those phenomena which have up to the present been interpreted through the assumption of semipermeable, partially permeable, and lipoidal membranes about cells."

Cell turgor, plasmolysis, and plasmoptysis (swelling until the cell wall is ruptured) are, he believes, all explicable on the basis of the increase of decrease of the affinity of the cell colloids for water.

R. S. Lillie has offered the following objection to an adsorption as against a membrane theory: "In adsorption equilibria are involved, as the characteristic equation indicates: i. e., the presence of a considerable quantity of a soluble substance in the adsorbed and presumably non-diffusible state requires also its presence in a free and diffusible state in sufficient concentration to maintain the equilibrium. Again, the chief colloidal and water-insoluble constituents of the protoplasm are readily hydrolyzable, and the conditions for their hydrolysis undoubtedly exist in all living cells; hence it can scarcely be doubted that the protoplasmic complex contains free amino-acids and sugars; it must also be assumed that at least part of the inorganic constituents exist in the form of ions free to diffuse, even though another part may be in combination, as ion proteid or otherwise. If these constituents were free to diffuse from the cell, it is evident that the existence of any stable chemical organization would be precluded, and the delicate balance of conditions on which the maintenance of normal life processes depends would be impossible."

In most of this Fisher would doubtless acquiese only instead of accepting Lillie's conclusion that "in order to prevent its own disorganization by outward diffusion of soluble constituents" living protoplasm has an investing membrane "impermeable—except under special and temporary conditions—to such diffusion," he would maintain that the whole phenomena is explicable on the basis of adsorption and the equilibria involved, the equilibrium of a given substance being not a fixed thing but subject to fluctuation with any variation in the external as well as the internal factors, just as the retention or loss of color in stained fibrin varies with different conditions in the surrounding liquid. For example, suppose that into three test-tubes the following substances be placed respectively: into the first, an aqueous solution of toluidin blue; into the second, a bit of fibrin and a similar solution of toluidin blue; and into the third, a bit of fibrin and a slightly acidulated solution of toluidin blue. The color will remain evenly distributed in the first, it will become very dense in the fibrin and scanty in the fluid in the second, but in the third the fibrin will remain entirely uncolored. The parallel to the conditions of the cell is obvious.

For an adequate appreciation of the merits of the arguments pro and con, original papers must be referred to, as no brief abstract can do the various authors justice. The papers of Overton[7], Lillie[8] and Höber[9] present in detail the one view, that of Martin H. Fischer[5], the other.

Chemistry of the Cell.

Since it is the proteins in general which seem to be most immediately linked with life phenomena the recent attempts toward their analysis and synthesis have been of unusual interest to the biologist. Enough has been determined regarding the consti-

---

5. *Loc. Cit.*
7. Nagel's *Handbuch der Physiologie,* Braunschmeig, II, 744; 1906.
8. *American Journal of Physiology,* 1905, 1909, 1910; *Biological Bulletin,* 1909; *Science,* 1909.
9. Weber den Mechanismus des Stoffaustausches bei den Zellen. *Ergebnisse der wissenshaftlichen Medizin.* Leipzig, 1910.

tution of proteins to show that they are as subject to the well established principles of configuration, polymerization, stereometry and the like as are the simpler organic compounds.

It has long been known that the various proteins are of very different orders of complexity. For example there are certain simpler types of the order of albumins, globulins and vitellins and other more complicated grades such as haemoglobin, which is a combination of haematin and globulin, glycoproteids (compounds of simple proteins with carbo-hydrates), or again even more complex ones such as the nucleoproteids which are resolvable into compounds of simpler proteins with nuclein, itself a compound of nucleic acid and an albumin or other free proteid.

The nucleoproteids are confined for the most part to the nucleus except for occasional overflows or discharges into the cytoplasm. But it should be observed that they are of the grade of simple proteins plus additional substances chiefly nucleins, and there is no reason apparent for not regarding the simpler cytoplasmic proteins as just as characteristic of the individual which bears them as the nucleins or the albuminous component which makes up the protein foundation for the nucleoproteid. The true nucleoproteids differ from other phosphorous-containing proteins, such as vitellin of egg yolk, and caseinogen, in at least the one respect that the so-called purine bases are characteristic cleavage products. Halliburton[10] has recently written a good non-technical paper on the chemistry of the cell nucleus.

Since the nucleins are so characteristic of the nucleus, nucleic acid being the chief factor responsible for the intense staining of chromosomes, any new discoveries regarding them are of exceptional interest to biologists, particularly those interested in the germinal mechanism of heredity. It is now a known fact that there are whole series of nucleins, varying according to the relative amounts of their nucleic acid and proteins.

Nucleic acid yields (1) phosphoric acid, (2) a group of bases termed purine bases, (3) a second group called the pyrimidine bases, and (4) a hexone carbohydrate. The purine bases, four in number

10. Science Progress Vol. IV, 1909.

(hypoxanthine, xanthine, adenine, guanine) have at different times borne different names such as nuclein bases, xanthine bases, and alloxuric bases, but they are now all termed purine bases because all have been shown to be derivatives of a fundamental "ring" compound called by Emil Fischer purine ($C_5 H_4 N_4$). Likewise the pyrimidine bases (cytosine, thymine, uracil) are all derivations of another ring compound, pyrimidine. As methods of analysis improve, the older idea that each nuclein has its own specific nucleic acid, is giving place to the idea that nucleic acid is in reality a substance of definite and constant composition.

The tentative view of Stendel regarding the constitution of the nucleic acid molecule is of considerable interest although it must be borne in mind that the formula may later have to undergo some revision. It is as follows:

```
O H — P — Sugar — Guanine
      |
O H — P — Sugar — Adenine
      |
O H — P — Sugar — Cytosine
      |
O H — P — Sugar — Thymine
```

That is, each of four enchained atoms of phosphorus is united on the one side to a hydroxyl group and on the other to a hexone carbohydrate molecule. Each hexone group is further linked to one of four different bases.

It has been found that nucleic acid and its salts under certain circumstances pass into a gelatinous or colloidal condition and Jones[11] has shown that in the case of the sodium salt the gelatinous and non-gelatinous conditions are readily convertible one into another. He sees in this fact a possible explanation of the physiological localization and migration o fnucleic acid in the cell.

The synthesis of nucleic acid in the cleavage cells after fertilization is one of the most important riddles to be solved by the cell-physiologist, for as Loeb[12] has pointed out in a most suggestive paper

11. *Journal of Biological Chemistry*, 1908.

12. On the Chemical Character of the Process of Fertilization and its Bearing upon the Theory of Life Phenomena. *Science*, Oct. 4, 1907.

"the most obvious chemical reaction which the spermatozoon causes in the egg" is "an eronmous synthesis of chromatin or nuclear material from the constituents of the cytoplasm." We have already seen that nucleic acid is one of the chief constituents of nuclein or chromatin.

Regarding Miescher's conclusion that lecithin, which is abundant in all eggs, is one of the substances from which nucleic acid is formed. Loeb has this to say: "The lecithin consists of two different groups of bodies, one being distearyl (or oleyl) glycero-phosphoric acid, the other being cholin. * * * The cholin can apparently not be utilized for the synthesis of nucleins, but the other constituent is able not only to furnish the phosphoric acid skeleton of the nucleic acid molecule, but also the carbohydrates. The fatty acid could be rendered available for this purpose by oxidation and we shall see indeed that phenomena of oxidation are the prerequisites of the synthesis of nucleins. * * * The question as to whether or not lecithin is the source of the phosphates and possibly some other constituents of the nucleic acid group can not be decided until synthesis of nucleic acid has been accomplished." He goes on to point out that "The fertilized egg cannot develop or increase the number of its nuclei unless an ample supply of free oxygen is present."

As to the chemistry of the proteins themselves great progress has been made in our knowledge in late years. Much of the advance has been due to the efforts of Emil Fischer[13] and his associates.

It is a familiar fact that the native proteins are readily broken down artificially by hydrolysis through a series of stages to simpler and simpler products. And it is known that essentially the same process occurs in normal digestion.

---

13. The results of Fischer's work from 1899 to 1906 have been published in book form "Untersuchungen über Aminosäuren, Polypeptide und Proteine," 1906.

See also "The Work of Emil Fischer and his School on the Chemistry of the Proteins," by R. H. Aders Plimmer, *Science Progress* Vol. II, 1907-8.

The sequence runs approximately as follows:

Proteins.
—Meta- or infra-proteins.
—Proteoses.
—Peptones.
—Polypeptids (a relatively small number of amino-acids linked together).
—Individual amino-acids, of which there is a great variety.

Because of the great abundance of the amino-acids and because of their universal presence as disintegration products of proteins, the conclusion has been reached that the protein molecule is built up in large part of a series of amino-acid polymers. These acids are closely related to the fatty acid series. They are in fact regarded as aminated fatty acids; that is, fatty acids given partial basic properties by the addition of NH_2 molecules. This possession of both acid and basic properties is what renders their ready linkage possible.

Emil Fischer's work upon carbohydrates and purine compounds had already become classic when he undertook the study of proteins. He first devised a method (the ester method) for the separation of the various kinds of amino-acids from one another and then set about synthesizing these units into proteid-like bodies.

Curtius and Goebel found many years ago that the ethyl ester of glycerine lost two molecules of alcohol when dissolved in water and became, to use modern nomenclature, glycerine anhydride,

$$\begin{array}{ccc} NH. & CH_2. & CO. \\ | & & | \\ CO. & CH_2. & NH. \end{array}$$

Fischer found that by boiling this substance with concentrated hydrochloric acid the so-called piperazine ring was split, giving the hydrochloride of the base $C_4H_8N_2O_3$. He termed this compound glycylglycine, calling the group $NH_2\,CH_2\,CO$ the glycyl group. Glycine being more readily prepared than other amino-acids, has been mostly used by Fischer in the synthesis of polypeptids. Depending upon the number of polymers involved he uses the terms di-, tri-, tetra-peptid, etc. He has succeeded in producing one of sufficient complexity to contain eighteen polymers. This octadecapeptid has three leucine and fifteen glycine radicals. In native proteins, with the possible exception of gelatin, which contains some 20 per cent of glycine, it is doubtful if such long glycine chains exist. The complex polypeptid in question, representing the most complicated combination ever obtained synthetically in which exact knowledge of its constitution has been retained, has a molecular weight of only 1213. It has been pointed out, however, that if the glycine residues could be replaced by leucine, phenylalanine or tyrosine residues, this weight would be doubled or trebled and would thus be as great as the normal for many native proteins.

Nearly one hundred polypeptids have been prepared so far. They resemble peptones in their appearance and in their reactions towards enzymes and various test reagents. Fischer, in fact, regards peptones as mixtures of polypeptids. Bodies of the same type as some of those he has constructed have also been isolated from natural organic substances. One of his synthetic forms, *l*-leucyl-triglycyl-*l*-tyrosin, seems to have all the properties of the albumoses. Furthermore, Abderhalden and several of his associates, maintain that when various of the polypeptids are injected into a living organism they are apparently utilized in metabolism in the same way that native proteins are.

The protein-splitting ferment trypsin does not produce hydrolysis of polypeptids which have a less number of glycine radicals than five. It is an interesting fact, moreover, that only certain of the higher polypeptids are hydrocyzed by trypsin. This gives an important clue for selecting suitable ones to use in synthetic experiments since probably only those acted upon by trypsin would represent the combinations most likely to occur in the natural proteins. Thus by studying the action of digestive ferments on polypeptids of known constitution, and at the same time on native proteins, it is hoped that sufficient insight will be gained into the chemical nature of the latter, to lead eventually to their synthesis at the hand of the chemist.

For a long time the optical activity (relation to the plane of polarized light) of compounds has been regarded as an important test in discriminating between those produced by vital processes and similar compounds prepared synthetically by the chemist. But Fischer has shown that both the optically active and inactive forms of these amino-bodies can be produced outside the body. Thus one of the last distinctions between "vital" and laboratory products has been swept away.

As regards the recent work of chemists on the proteins, then, if the reviewer may quote from one of his own papers[14] now in press, "The results point clearly to the conclusion that the peptones and higher proteins are huge molecules formed chiefly of amino-acid molecules linked together by NH and CO affinities left unsatisfied as a result of processes comparable to dehydration. Such a protein molecule may perhaps be represented as a main chain or ring, of which the respective links are amino-acid "nuclei." Glycocoll, NH_2CH_2COOH, for instance, would through dehydration have for its nucleus in such a chain—$NH.CH_2.CO$—. Furthermore, since one H of the CH_2 of such "nuclei."

$$\text{(e. g., —NH.}\underset{\displaystyle \text{H}}{\overset{}{\underset{|}{\text{CH}}}}\text{.CO—)}$$

can be substituted by various compounds (acetic acid, butane, methyl-paraoxybenzene, etc.) we are led to conclude that to each link of the protein chain, a side chain, differing in constitution in different cases, is attached or is attachable by replacement of this hydrogen atom. The well known instability of living protein would seem to be due to the fact that the chemical systems in such a giant molecule are never fully saturated at any one time, so that there is continually an adding and detaching and shifting of side-chains with perhaps at times more fundamental shifts or replacements in the amino-acid "nuclei" themselves. Quantitative and qualitative differences of proteins would seem to depend fundamentally on the kind and amount of the constituent amino-acids and secondarily on the chemical nature of the various side-chains.

14. *American Naturalist*

Probably the scheme as outlined is much simpler than the true conditions in the protein molecule, but it will serve as a sort of diagram of the relations which exist there. It is probable, too, that the conditions in different proteins vary greatly in complexity. The chief point to be emphasized is the fact that the results of many investigators bear out this general conception of the protein molecule."

There is a growing interest in the properties and constitution of certain compounds of labile nature termed lipoids, of which lecithin and cholesterin are probably the best known. Flexner and Noguchi, for instance, have shown that the haemolytic action of cobra venom on red corpuscles goes on only in the presence of blood serum, and Kyes identified the activator in the serum as lecithin. He found, furthermore, that cholesterin has the property of preventing the activation of cobra venom by lecithin. The interest in these bodies, particularly by workers in experimental medicine has in consequence, been greatly intensified.

Certain groups of lipoidal substances, the phosphatides particularly, are found very frequently in both animal and plant organs in combination with various proteins, carbohydrates, glucosides and alkaloids, but whether the combination is a definite chemical union or whether, as most investigators seem inclined to believe, it is due to the adsorbing power of the colloidal phosphatides, is unknown. Perhaps the lecitho-protein obtained from the yolk of eggs has received most attention.

Cholesterin which belongs to another class of lipoids characterized by their freedom from both phosphorus and nitrogen, seems to be a constant and therefore presumably an essential constituent in the cells of both plants and animals. Recent investigations tend to show that it has little in common with fats but belongs to the so-called "terpenes," a peculiar class of substances found chiefly in plant secretions. Some are inclined to look upon its presence as a protective function against the attacks of toxins, whether autotoxins or of external origin. It has been found by Przibram, for example, that the serum of animals fed on cholesterin develops a resistance against the haemolytic action of saponin eight times greater than exists in the normal animal.

A few investigators, such as Bang, believe the proteins have been overestimated and the lipoids underestimated as the "carriers of life." Speaking of lecithin in particular, Rosenheim[15] has this to say: " * * * it is quite possible that lecithin may be not only an activator for the assimilation of toxin, or an amboceptor which anchors the toxin on to the cell it attacks, but in a more general sense it may play a *role* in the same sort of way in relation to the safe anchorage of nitrogenous substances of food value, which are important for cell life. The latest researches on ferment action have clearly shown that ferments are not present in cells in the active state but as so-called pro-ferments. To produce their effect another—chemically so far unknown—substance is necessary; and that this substance may be lecithin (or a similar lipoid) is a view that is gaining ground."

Some Matters of Terminology.

Along with the advances in our knowledge of cell structure have come a number of new terms. It seems advisable, therefore, to indicate the meaning of some of those most frequently encountered in current literature. The unreduced number of chromosomes in the body cells and early germ cells is now usually spoken of as the *diploid,* and the reduced, as the *haploid* number of chromosomes. The term *synapsis* which originally referred to the entire process of the peculiar contraction of the spireme and pairing of the chromosomes which occurs during one stage of the maturation period is now restricted so as to mean only the actual pairing, the contraction phase being indicated by the term *synizesis.* The end-to-end pairing of chromosomes is termed *telosynapsis,* the side-to-side pairing, *parasynapsis.* The *accessory* or *odd chromosome* originally found in the spermatogenesis of certain insects and looked upon as of possibly great significance in sex determination, is variously termed, *heterochromosome, monosome, heterotropic chromosome, idiochromosome* and *X-chromosome.* Montgomery also designates the ordinary chromosomes in which there are no marked differences in be-

15. The Biochemistry of Animals and Plants. *Science Progress* Vol. III, 1908, P. 117.

havior as *autosomes,* and all chromosomes of different behavior he terms *allosomes.* Allosomes that occur in pairs in the spermatogonium he calls *diplosomes.* The term *maiotic phase* is used by some workers, more particularly botanists, to indicate the series of nuclear changes involved during the so-called "maturation period." Certain chromatin-like bodies which may be present in the cytoplasm outside of the nucleus are termed *mitochondria* or *chondriosomes.*

Individuality of Chromosomes.

The question of the persistence of the individuality of chromosomes through successive divisions, first made prominent by Rabl and Boveri and later by Moenkhaus[16], Tennant[17], and others, continues to be a pertinent topic. If the term individuality is used in the sense of genetic continuity as expressed by Wilson[18], that is, that each chromosome bears a genetic relation to one only of the previous generation, the view is pretty generally accepted by cytologists, although various investigators have pronounced adversely upon it. An adverse criticism based upon certain fact of amitosis will be found in a paper by Child[19]. In a recent paper of Morgan[20] on "Chromosomes and Heredity" there is a good general discussion of the whole topic. And an interesting analysis of the scepticism of Della Valle and other opponents of the theory is rendered by Montgomery[21] in his paper "On the Dimegalous Sperm and Chromosomal Variation of Euschistus, with Reference to Chromosomal Continuity." A recent series of chromosome studies by Miss Bonnevie[22] are also of much interest in this connection. Among botanists Overton[66], for instance, finds that in both the somatic and the germ cells of certain plants the chromosomes do not lose their identity during the periods between divisions, but persist as visible "pro-chromosomes" arranged in parallel pairs with apparent linin intervals.

16. *American Journal of Anatomy,* III, 1904.
17. *Biological Bulletin,* Aug. 1907.
18. *Journal of Experimental Zoology,* VI, 1909.
19. *Anatomischer Anzeiger,* 1907.
20. *American Naturalist,* Aug. 1910.
21. *Archiv fur Zellforschung,* V, 1, 1910.
22. See Vols. of *Archiv fur Zellforschung* for 1908-1910.
66. *Annals of Botany,* 23:19-61, 1909.

Chromosomes and Heredity.

There is an undeniable tendency at present to swing away from the older extreme view which regards the nucleus, or more particularly the chromosomes, as the exclusive mechanism of inheritance to the view that looks upon the new individual as the resultant of elaborate interactions of nucleus and cytoplasm, and which attributes a monopoly of inheritance material to neither one nor the other. There is also a manifest inclination to emphasize the importance of quantitative factors in development. The field is too great to cover here in any detail but general discussions will be found in recent easily accessible papers of Morgan[20], Guyer[23], and Conklin[24].

Having in mind the alleged fact that offspring inherit equally from each parent, various workers have laid stress upon the striking parity between the chromosomes of male and female pronuclei as an incontrovertible indication of their preeminence as bearers of the so-called hereditary characters. The validity of the assumption that offspring inherit equally from each parent has, however, not gone unchallenged. Guyer[25] has cited adverse evidence and has contended that there is in fact no justification for the assertion that the entire quota of characters which go to make up a complete organism are inherited from each parent equally. Indeed, many of these characters—and these in general the most fundamental—are such as are common to both parents and there is no way of measuring how much comes from each parent. We know from the fact of artificial parthenogenesis that an egg with a haploid number of chromosomes has all the material necessary to build up a complete organism but we have no such evidence for the male gamete. Looking upon cytoplasm and chromosomes as responsive mechanism and inciting agent respectively we can readily see how if one set of chromosomes and the cytoplasm can cooperate to produce an organism, a second set of chromosomes could so assume or modify the

---

20. *Loc. Cit.*

23. Deficiencies of the Chromosome Theory of Heredity. *University of Cincinnati Studies,* Sept. 1909. See also, Nucleus and Cytoplasm in Heredity, *American Naturalist* (in press).

24. The Mechanism of Heredity. *Science,* Jan. 17, 1908.

25. *Science,* June 28, 1907.

functions of the first as to share equally in the outcome. Such parity, however, would be rather a question of equal inheritance of the decisive factors of individual traits than of the entire organic mechanism. The only measurable things that are contributed equally in inheritance are the sexual and specific differences which top off as it were the more fundamental features of the organism.

This writer is not alone in maintaining that there is a disparity in the inheritance from male and female for in the following year we find Conklin[24] remarking as follows: "In short the egg cytoplasm fixes the type of development and the sperm and egg nuclei supply only the details." Again, "So far as those characteristics are concerned which appear late in development, it is highly probable that there is equality of inheritance from both parents, but in the early and main features of development, hereditary traits, as well as material substance, are derived chiefly from the mother."

From the foregoing it will be seen that while there is no contention that the chromosomes are not of great importance in inheritance, there is a protest against attributing inordinate importance to them.

Apart from the apparent association between sexuality and the "accessory" chromosome, and the visible evidence of chromosomal individuality as shown by constancy in the relative sizes and shapes of the individual chromosomes in the cells of certain species, there are also indications of differences in the physiological behavior of the separate chromosomes, each probably representing certain activities not evinced by the others. Boveri's[26] remarkable experiments with dispermic eggs of the sea-urchin afford strong evidence to this effect. In such eggs he found that the mitotic mechanism of the first cleavage is usually atypical and the chromosomes are distributed in unequal numbers to the three or four blastomeres which result from this cleavage. When such blastomeres were isolated, while various ones developed to a greater or less extent, only those developed normally which contained one full haploid set of chromo-

---

24. *Science,* Jan. 17, 1908.

26. Mehrpolige Mitosen als Mittel zur Analyse des Zellkerns. *Vehr. d. Phys. Med. Ges. zu Wurzburg,* XXXV.

somes. He concluded that for normal development to take place one of each kind of chromosome must be present.

To cite but one more line of suggestive evidence regarding the possible relations of individual chromosomes to heredity, attention may be called to the work of Gates[27] who has shown in his various papers that the mutants of *Oenothera Lamarckiana* are characterized by differences of chromosomal content.

Chromosomes and Mendelism.

In recent years considerable attention has been centered in the chromosomes as the possible vehicles for the conveyance of those factors which determine the Mendelian characters. Obviously, if hereditary traits are represented in the chromosomes, then the familiar reduction phenomena in which half the chromosomes are set apart in one cell and half in another would supply exactly the kind of mechanism that is necessary for such a separation of pairs of parental characteristics as transpires in the Mendelian phenomena.

In 1900 evidence was published by Guyer[28] showing that in the spermatocytes of hybrids when the period for synapsis had arrived, a peculiar chromosomal segregation manifested itself. The chromosomes instead of pairing showed a decided tendency to remain in two groups. This was interpreted as being due to an incompatibility between the chromosomes of the maternal and paternal species, the implication being that synapis, or pseudo-reduction as it was then very generally called, in normal forms consisted in a pairing of maternal with paternal chromosomes. The same investigator[29] had shown earlier that in hybrid doves there is a marked tendency for individuals of the third generation to revert to grandparental forms (a phenomenon we recognize as Mendelian today). Putting all these facts together it was pointed out how the behavior of the chromosomes of hybrids afforded a possible explanation of such returns.

Soon other and more direct evidence of the pairing of maternal and paternal chromosomes during synapsis was forthcoming as the

27. See Bot. Gazette for 1907-08, and Science Jan. 31, 1908.
28. *Science*, Feb. 16, 1900.
29. *Zoological Bulletin*, II, No. 5, 1899.

result of Montgomery's[30] and Sutton's[31] studies on non-hybrid forms. Species were found in which the chromosomes differ among themselves in size and appearance. Furthermore, the fact was soon established that in early germ-cells the chromosomes exist in pairs, one member of each pair being of paternal the other of maternal origin, and that during synapsis it is the corresponding members of a pair which unite. The ensuing reduction division simply brings about their separation and segregation into different cells, each cell receiving one full set of single chromosomes. Since any one pair of chromosomes at the reduction phase presumably lines up for division wholly by chance as to which member of the pair lies toward a given pole of the spindle, the cells which result from the division will in general contain some chomosomes of maternal and some of paternal orogin.

In the mean time Guyer[32] had extended his observations to the germ-cells of plants and expressed the view that "the extreme variability seen in the offspring of fertile hybrids was possibly to be attributed to this variability in chromatin distribution." In a later paper[33] which was an abridgement of an earlier (1900) thesis he restated his views regarding the "separation of the paternal and the maternal chromosomes which had fused during synapsis" and it was pointed out how, in the case of fertile hybrids the chromosomes (assuming them to be the bearers of hereditary qualities) would segregate at the reduction period and that as the result of this separation at the subsequent period of fertilization "there are four combinations possible, and two of the four would result in the production of mixed offspring, while only one combination could result in a return to one of the ancestral species." In 1903 he[34] correlated his conclusions with the so-called Mendelian principles, which had had their renaissance in the mean time, pointing out

30. A Study of the Chromosomes of the Germ Cells of the Metazoa. *Trans. Amer. Phil. Soc.* XX, 1901.

31. On the Morphology of the Chromosome Group in Brachystola magna. *Biological Bulletin,* 1902.

32. Some Notes on Hybridism, Variation and Irregularities in the Division of the Germ-cell. *Science,* Apr. 4, 1902.

33. *Bulletin 21, University of Cincinnati.* Nov. 1902.

34. *Cincinnati Lancet-Clinic,* May 9, 1903.

that "where reversions follow the Mendelian law, the germinal incompatibilities must be narrowed down to the qualities themselves rather than confined to the respective germ-plasms as a whole. These qualities must separate and each take up its abode in a different germ-cell irrespective of whether the other qualities of that particular germ-cell are of a different parentage or not."

Meanwhile Cannon[35] and Sutton[36] came to the conclusion likewise that the mechanism of chromosome reduction affords a possible explanation of Mendelian segregation if we assume that each character which Mendelizes is carried by a particular chromosome. This hypothesis was also supported by both Wilson and Boveri. While these earlier papers are only the first approximations toward present ideas regarding these matters, the historical development of the situation is perhaps of some interest. One obvious objection to the idea that each particular factor for the production of a Mendalian character is confined to a single chromosome lies in the possibility that the number of chromosomes is not as great as the number of characters which Mendelize separately. If we assume that the factors for a large number of characters reside in the same chromosome, then on a theory of strict chromosomal individuality, we should have to suppose that the characters in question must all Mendelize together, and we have not as yet evidence to justify such a conclusion. We seem to be approaching more or less closely at present the conception that each chromosome affects to some extent the whole process of development and is not merely an assemblage of "unit characters." Various writers have recently discussed the germinal basis of Mendelism from interesting points of view and the student will do well to read papers of Holmes[37], Spillman[38], Gates[39] and Morgan[20] in this connection.

---

35. *Bull. Torrey Club,* 1902; and *ibid.* 1903.
36. *Biological Bulletin,* 1903.
37. The Categories of Variation. *American Naturalist,* May, 1909.
38. Mendelian Phenomena without deVriesian Theory. *Am. Nat.* Apr. 1910.
39. The Material Basis of Mendelian Phenomena—*Am. Nat.* Apr. 1910.
20. Loc. Cit.

THE ACCESSORY CHROMOSOME AND SEX.

Nothing of a cytological nature has attracted more universal attention during the last eight or nine years than the discoveries and interpretations centering about a peculiar chromosome or chromosome-group variously designated as the "accessory chromosome" (McClung), "odd chromosome," heterochromosome" or "monosome" (Montgomery), the "heterotropic chromosome," "idiochromosome," and X-chromosome, (Wilson). This element so behaves in one of the maturation divisions of the spermatocytes (in some forms in the first, in others in the second division) that an asymmetrical distribution of the chromosomes follows, resulting in the production of two equal classes of spermatozoa: viz., those which contain the accessory, and those which do not. It is not always a simple element but, depending upon the species, there may be one, two, three, four or five separate chromatic bodies. It has been clearly demonstrated in insects at least that eggs fertilized by spermatozoa which possess this accessory chromosome or chromosome-group develop into females, those fertilized by spermatozoa which do not possess it develop into males. With this obvious association between a special chromatic element and sexuality, interest has waxed exceedingly keen in all researches bearing upon the problems involved.

Aside from the evidence of what the accessory chromosome itself does or does not do, the great mass of facts brought together in various other investigations points convincingly to the conclusion that under normal conditions at least, sex is automatically determined by physiological factors within the germ-cells and not as a response of the developing organism to stimuli from without.

The reader must have clearly in mind the conditions which prevail during maturation. In sexually produced organisms the ordinary cells of the body and the primitive germ-cells have the double or *diploid* group of chromosomes. The ultimate germ cells, however, when ready for fertilization possess only a single or *haploid* group, the double condition having been lost during the reduction division. That is, apart from the accessory, which may be present in one half of the male gametes, the mature germ-cell has only half as many chromosomes as the other cells of the body. The diploid condition is restored of course at fertilization.

Historically, McClung[40] writing in 1902 on the spermatogenesis of certain Orthoptera was the first to announce and support the view that the accessory chromosome is concerned in the determination of sex. For although Henking[41] in 1891, discovered a similar dimorphism of spermatozoa in *Pyrrhocoris*, a Hemipteran, and Paulmier[42] did likewise in 1899 working on *Anasa*, apparently it did not occur to either of these workers that the phenomenon was associable with sex. The cases studied by all of these earlier investigators belonged to the simplest type of accessory, namely, that in which, in one of the maturation division periods, a particular chromosome instead of dividing passes intact to one pole. As a result half of the spermatozoa receive one more chromosome than the other half. McClung regarded the accessory as "the bearer of those qualities which pertain to the male organism, primary among which is the faculty of producing sex cells that have the form of spermatozoa." Since the maternal number of chromosomes was unknown to McClung and the number in the male was odd instead of even, he considered that the extra chromosome was an additional one and was male producing. And in fact in the same year Sutton described in the female of *Brachystola* twenty-two chromosomes, that is, one less than in the male. Later studies however showed that Sutton was mistaken in his count and that there is in reality one more chromosome in the female than in the male of *Brachystola;* viz. twenty-four.

In 1905-06 the studies of Stevens[43] and Wilson[43] on various species of insects showed that it was not uncommon for the accessory chromosome to possess a mate usually much smaller than itself. These two chromosomes come into close contact during synapsis and in the ensuing division diverge to opposite poles so that while the resulting spermatozoa have the same number of chromosomes, there is still a dimorphism, since half of them have received the

40. *Biological Bulletin*, III, 1902.
41. *Zeitschrift fur wissenschaftliche Zoologie*, 1891.
42. *Journal of Morphology*, XV, suppl. 1899.
43. See the series of papers by these authors in the *Journal of Experimental Zoology*.

larger and half the smaller member of this asymmetrical pair. Wilson at first called them the large and the small idiochromosomes but in recent papers designates them as the X and Y elements.

He believes it very probable that, the first type, in which there is only the accessory or X-element, has arisen by the gradual disappearance of the Y-element, for in different species various graduations are found between those in which the Y-element is almost or quite as large as the X-element to those in which it is very minute. In such forms as *Nezara* and *Oncopeltus* the two elements, X and Y, are of the same size, and on the basis of this fact Wilson suggests the possibility that there may be many other forms which possess X and Y chromosomes but in an indistinguishable condition because they are not visibly different from the other chromosomes.

Still further complications arise from the fact that the X-element in some species is double in others triple in still others quadruple and in one form (*Acholla*) possibly quintuple. The multiple element, however, in every case behaves as a single X-element, pairing at the reduction period with the single Y-chromosome when such exists, and passing intact as a group to one pole while the simple Y-element passes to the other. Payne[44] regards such compound elements as components of what was originally a single large chromosome.

In late years numerous discoveries of similar facts have been made by a rapidly increasing number of workers until now this dimorphic condition of spermatozoa is known to be of much wider prevalence than was suspected by the earlier workers who confined their studies to insects. Among invertebrates the X-element in varying degrees of structural complexity has been recorded from diverse groups of insects (McClung, Sutton, Stevens, Wilson, Montgomery, Gross, Lefevre, McGill, Dederer, Davis, Gutherz, Nowlin, Boring, Jordan, Morrill, Payne, Morgan, von Baehr, Morse, Randolph, Nichols, Cooke, Browne), myriapods (Blackmann, Medes), arachnids (Wallace, Berry), and nematodes (Boring, Boveri, Gulick, Edwards). In echinoderms (Baltzer) an interesting reversal of conditions has been found in that the eggs instead of

44. For a discussion of such cases in Insecta see Payne's paper; *Biological Bulletin*, 1909. XVI., P. 119.

the sperm possess the odd element and show the characteristic dimorphism.

Recently the field has been extended to the vertebrates, X-elements having been recorded from such diverse forms as the guinea, chicken, rat and man (Guyer[45]) the armadillo (Newman and Patterson[46]) the opossum (Jordan[47]), and the guinea-pig (Stevens[48]).

Since the X-element may or may not be associated with a Y-element, the existence of the latter seems to be a wholly capricious one, at least as far as sex production is concerned, and for the sake of simplicity its presence has been ignored in most discussions. So far absolutely no hint as to its significance has come to light.

The conclusion that sex-production is based on chromosomal dimorphism of the spermatozoa involves the assumption that the mature eggs are all alike as regards their chromatin content. The condition of the eggs in this respect has not been widely investigated as yet but in a number of cases it is known that after the reduction division the eggs do all contain chromosomes similar in appearance and number. Moreover, before reduction, the oögonia of these individuals always have an even number of chromosomes, the unpaired chromosome which makes the number odd in the male being here represented by two chromosomes of equal size. A corresponding difference in number and appearance also exists between the somatic cells of the male and female.

This fact has been definitely established in phylloxerans (Morgan), aphids (Stevens, von Baehr, Morgan), the nematode *Heterakis* (Boveri, Gulick), and in several coreid Hemiptera (Morrill[49]).

Morrill has found that the female pronuclei are not dimorphic in the four species he studied and that in each species the female pronucleus contains a group of chromosomes similar to those of the X-bearing spermatozoa of that species. He concludes as fol-

45. *Anatomischer Anzeiger,* XXXIV, 20-21, 22-23, 1909. *Biological Bulletin,* XIX, 4; Sept. 1910.

46. *Journal of Morphology,* XXI, 3.

47. *Science,* March 10, 1911.

48. *Biological Bulletin,* Jan. 1911.

49. For a discussion and bibliography see Morrill's paper in the *Biological Bulletin,* XIX, July, 1910.

lows: "In the cleavage and early blastodern nuclei of *Archimerus, Anasa, Chelinidea* and *Protenor,* the chromosomes are perfectly distinct and can be counted as readily as those of the gonads. Two types of embryos are found, one having an odd and the other an even number of chromosomes, these numbers being respectively the same as occur in the spermatogonia and oögonia. Accordingly it seems fair to conclude that the former are males, the latter females, and it thus becomes possible to distinguish the sex of an embryo by counting its chromosomes."

A formidable difficulty seemed at one time to present itself in the case of phylloxerans and aphids where females only are produced from fertilized eggs. If, it was argued, there are two classes of spermatozoa, male-producing and female-producing, why are not both males and females produced when the eggs of these forms have been fertilized? The remarkable discovery was made, however, by Morgan in *Phylloxera* and independently by von Baehr in *Aphis,* that while half the spermatocytes do receive the X-element (single in *Aphis,* double in *Phylloxera*), and half do not, the latter abort and never come to maturity. Thus only the X-class, or "female-producing" spermatozoa ever become functional. On the other hand, both males and females develop from parthenogenetic eggs. The interesting discovery was made both by Morgan and von Baehr that the males have the characteristic lesser number of chromosomes, the female the increased number. But how is this dimorphism produced, since it is well known that such parthenogenetic eggs form but one polar body and have no reducing division? Morgan's work makes it practically certain that the difference in chromosome number is brought about at the time of the extrusion of the single polar body, half the eggs retaining one more chromosome than the other half. Here, then, in these parthenogenetic forms, is an example of sex-production, in which presumably something in the egg itself, not fertilization, is the determining factor of sex. Even before the extrusion of the polar body, indeed, the male producing egg is distinguishable by its smaller size.

But granting that the accessory chromosome or chromosome-group when it exists is always associated with sex-differentiation, the important query arises as to just what the relationship is between the two. This problem is a very intricate one and has led to such extensive discussions and subtelties o fdistinction that a resumé brief as that necessitated by the limits of the present review must be inadequate. Fortunately the reviewer can feel himself absolved somewhat in this respect because of recent excellent critiques covering this entire field. By reading certain papers of Wilson[50], Morgan[51], Montgomery[52] and Stevens[53] published during the past two years the general student can soon bring himself practically up to date on the questions at issue.

As to what the X-element really signifies in connection with sex at least four possibilities have been suggested: namely, (1) that it is an actual qualitative sex-determinant; (2) that sex is determined by purely quantitative conditions of the chromatin; (3) that the X-element is merely sex-accompanying and not sex-producing; (4) that sex is the resultant of several essential factors and is not established unless all work together, the X-element being the *decisive* factor.

The assumption that the X-element is an actual sex-determinant operating qualitatively is at first sight the simplest explanation but in reality it involves various complications of which we have no evidence; such, for example, as selective fertilization. For we have seen that eggs which are fertilized by spermatozoa carrying the X-element always develop into females, those fertilized by spermatoza of the other class always producing males. This leaves us in the predicament of having to account for the origin of the new X-element of these males. Obviously it must come from the egg, and this being true, then the two egg chromosomes which before

50. a. Recent Researches on the Determination and Heredity of Sex. *Science* Jan. 8, 1909.
b. The Chromosomes in Relation to the Determination of Sex. *Science Progress*, Apr. 1910.

51. a. A Biological and Cytological Study of Sex Determination in Phylloxerans and Aphids. *Journal of Experimental Zoology*, VII, 2; 1910.
b. Chromosomes and Heredity. *American Naturalist*, Aug. 1910.

52. Are Particular Chromosomes Sex Determinants? *Biological Bulletin* XIX, June 1910. (In connection with this read also a note by Wilson in *Science*, Aug. 19, 1910).

53. Further Studies on Heterochromosomes in Mosquitos. *Biological Bulletin*, XX, 2; Jan. 1911.

the reduction division correspond to the odd chromosome of the male, must be different one from another. Hence, inasmuch as they separate at reduction, there must be two classes of eggs, one class containing a male determinant and one a female determinant. The one containing the male determinant would always have to be selected by the sperm *without* the X-element, since only that combination can give rise to a male. Eggs containing the female determinant would have to be fertilized by the sperm carrying the X-element (which we have just seen must be the *male* determiner since it originally determined the male from which it is derived). Hence we are forced to the further assumption that in the egg so fertilized, there is a female determinant native to the egg and a male determinant brought in by the sperm, and that the former is dominant to the latter, producing a female individual.

As to an explanation based on the purely quantitative relations of the chromatin, in the majority of cases a female does develop from those eggs which have received the most chromatin (i. e. the accessory, or the larger X-element where X and Y-elements are present) but unfortunately for this theory there are cases known in which the Y-element is of greater mass than the X-element, yet nevertheless eggs receiving the X-element develop into females.

If we accept the third possibility, that the X-element is merely sex-accompanying, we still have thrown upon us the burden of determining what its function is if it is not sex-determination. Miss Stevens[53] makes the suggestion that the differentiation of an X-element or of unequal X and Y-elements, "may be directly related to sex-limited inheritance of certain characters," the idea being apparently that sex itself is not necessarily determined by the X-element but that certain characters which go with it are.

As to the fourth possibility, the fact that in certain parthenogenetic forms the sex of the forthcoming offspring can be foretold from the size of the egg before the X-element has become set apart shows that in these cases at least, the X-element is not the only factor concerned in sex-production, although it may be the *decisive* factor.

Professor Wilson[50] has recently expressed an inclination to accept a modified quantitative conception as the more intelligible view as far as dioecious organisms are concerned. He states as a plausible tentative hypothesis the view that "the presence of one X-element means *per se* the male condition, while the addition of a second element *of the same kind* produces the female condition." It is to be noted that the idea of quantity here is restricted to a particular *kind* of chromatin, viz. that of the X-element, and is not a mere question of the presence of a greater total amount of chromatin. In cases such as the sea-urchin where seemingly the egg instead of the sperm bears the X-element, the matter might be explained upon a similar quantitative basis by inferring that the female condition is determined by the presence of one X-element, the male condition by the total absence of an X-element. This second inference is not at all out of harmony with some known facts of Mendelian inheritance. For in crossing certain horned and hornless breeds of sheep, if we represent the horn-determining factor by H, then for the female to have horns the factor must be present in the duplex (HH) condition, the simplex condition (H) leaving her hornless. However, the presence of the simplex condition in the male results in the presence of horns, the total absence of H being required for hornlessness.

The Dynamics of Cell Division.

The various processes concerned in cell division continue to bring forth an unending series of new facts and new interpretations. There seem to be almost as many divergent views and shades of opinion as there are separate workers on these problems. It is evident that while the division of the nucleus and of the cytoplasm are usually closely interrelated, they are really two distinct phenomena inasmuch as either mitosis or amitosis may occur without subsequent division of the cytoplasm, and on the other hand, as shown by McClendon[54] who succeeded in securing segmenta-

53. Loc. Cit.
50. Loc. Cit.
54. *Arch. f. Entwicklungsmechanik*, XXVI, 4, 1908.

tion of Echinoid eggs deprived of chromatin, repeated cytoplasmic division may take place without the presence of the nucleus.

Because of the multiplicity of interpretations the only procedure open to the reviewer seems to be to cite a few representative papers in which discussions and bibliographies may be found.

The tendency in explaining mitosis has been to get away from the original idea of contracts or pushing fibers and to seek light along the lines of electro-static displacement (Gallardo, Lillie), osmotic currents (Leduc), or osmotic diffusion (Bütschli, Rhumbler). Some workers have confined their attention to the division of the cytoplasm, particularly in early cleavage (R. S. Lillie[55], Robertson[56], McClendon[57], etc.), while others have had in mind more the nuclear phenomena or some special phase of it such as the nature of the spindle (e. g. F. R. Lillie[58], Morgan[59], and Spooner[60]). Loeb's[12] address delivered at the International Zoological Congress at Boston in 1907, contains much matter which bears on the problems of cell division.

Amitosis.

During the last few years it has become evident that amitosis is a much more common method of division than was formerly supposed, and it has been shown, furthermore, that mitosis may frequently follow it even in the germ cells. Child[61] has perhaps made the most extensive studies of amitosis in recent times. He reports its occurrence in representatives of six different phyla of the animal kingdom. A very recent review and discussion of the literature of amitosis will be found in a paper by Richards[62]. He is not in agreement with Child as regards *Moniezia.* Wieman[63] also con-

55. *Biological Bulletin* XVII, 1909.
56. *Archiv fur Entwicklungsmechanik,* XXVII, 1909.
57. *American Journal of Physiology,* XXVII, 1910.
58. *Science,* June 12, 1908. Also *Biological Bulletin,* 1909.
59. *Journal of Experimental Zoology,* Nov. 1910.
60. *Journal of Experimental Zoology,* Jan. 1911.
12. *Loc. Cit.*
61. See his series of studies in the *Biological Bulletin* for 1907, and also the *Anatomischer Anzeiger* for 1904 and 1907.
62. *Biological Bulletin,* Feb., 1911.
63. *Journal of Morphology.* Vol. 21, No. 2, 1910.

tributes some new facts and offers some interesting suggestions in a late paper. He suggests that variation in the normal oxygen supply may be responsible for amitosis. To quote him directly: "The occurrence of amitosis at corresponding stages in the germ cells of both sexes is believed to be due to a periodic fluctuation in the nutritive supply of the cells brought about by a stimulus to a rapid cell division which causes a temporary derangement in the normal metabolism. In the ovary the disturbance is merely transient; but in the testis it is more prolonged for the reason apparently that it is here involved in the formation of cysts, a process that in the species under consideration is always accompanied by rapid cell multiplication.

"In the nurse cells the initial cause of amitosis is probably the same; but in this instance it is carried to an extreme, so that a permanent change in metabolism occurs.

"Amitosis and mitosis are believed to stand for the extremes of a continuous series; the different configurations of the division figures being due to the different types of metabolism represented."

Nemiloff has indicated two localities in which the student will find readily observable amitotic divisions; namely, the layer of lymphoid tissue of the amphibian liver, and the large superficial cells of the transitional epithelium in the bladder of mammals. In the case of the amphibian liver, however, the condition seems to be a rather complicated one. First a depression forms in the side of the spherical nucleus and continues to deepen until the nucleus is completely perforated and exists in the form of a ring which later fragments into two or more daughter nuclei. A centrosome and attraction sphere are frequently observable but the part they play in the division is not clearly understood.

In plants we find processes of amitosis paralleling those of animals. Griggs[64], for instance, in his paper on "Some Aspects of Amitosis in Synchytrium" reports that at certain periods direct divisions of the nucleus are of more frequent occurrence than indirect divisions. He recognizes at least two different types of amitosis: "(1) The karyosome of the parent nucleus gives off a small

64. *Botanical Gazette,* Feb. 1909.

karyosome which migrates through the nuclear membrane, forms a vacuole and a membrane about itself, and becomes an independant small nucleus, the whole looking like a budding yeast plant. This process is repeated until the parent nucleus is converted into small nuclei, often forming a definite group. (2) The membrane of the parent nucleus dissolves, and the karysome fragments into a number of pieces, each of which becomes a new nucleus, thus giving rise to a morula-like cluster of nuclei.

"These nuclei at later stages undergo mitosis and their descendants form spores and become the nuclei of succeeding generations."

Intracellular Canals.

In a recent paper Bensley[65] gives an interesting discussion of the canalicular apparatus of animal cells. Ever since Golgi in 1898 discovered what he believed to be an internal reticular structure in nerve cells investigators have been much interested in more or less similar appearing structures in many other kinds of cells. It seems not improbable that they may be shown to be of universal occurrence in animal cells. Some investigators have maintained that they are a real network, others, and chief among them Holmgren, that they are a series of tubular "juice" canals. Bensley has extended these studies to plant cells (Root-tips of *Allium, Lilium,* and *Iris,* and the tapetum of the lily) and after a careful study of the living as well as the fixed material he concludes that, in these plants, the true condition during life of this seeming network is that of a canalicular system, the familiar post-mortem vacuolated condition being of secondary origin. Since the corresponding system in the animal cell behaves similarly when treated by the same methods he believes himself justified in stating as a working hypothesis "that the network of canals found in many animal cells is the physiologic and morphologic equivalent of the vacuolar system of the plant cell." According to Retzius and others the system in animals represents a series of intracellular nutritive or drainage canals which are directly related with the lymphatic system.

65. On the Nature of the Canalicular Apparatus of Animal Cells. *Biological Bulletin,* XIX, Aug. 1910.

As this review has already far transgressed the limits set upon it by the editor, the reviewer reluctantly turns his face from the numerous important topics which he had hoped to touch upon but must now dismiss. Bearing in mind the fact that the paper is more for the general student than for the specialist the writer has confined his references as much as possible to general articles and particularly to such as are written in English. Some phases of the work may seem to the reader to have been unduely emphasized to the exclusion of more strictly cytological problems. This has been done intentionally, however, because it was felt that a digest of this newer and less familiar field, in which the literature is scattered and is for the most part highly technical, would be more welcome and of greater use to the general biological reader than a resume of the more familiar and conventional cytological problems. For in the uncertain realm of biology one certainty stands forth conspicuously; namely, that the biologist of the future who expects to deal with the dynamics of the living cell must be versed in colloidal phenomena and other physico-chemical lore.